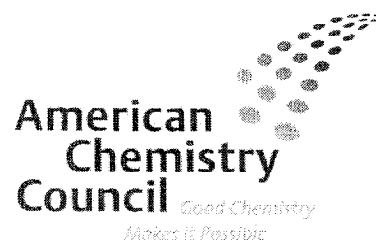


COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR



September 26, 2003

Via U.S. Mail and E-mail

Ms. Marian L. Horinko, Acting Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

**Re: Hydroquinone Precursors and Derivatives Panel-Diisopropylbenzene Task Force Consortium No.
Diisopropylbenzene Category Justification and Testing Rationale
Response to EPA's Comments of April 8, 2003 on ACC Panel's Original Submission of November 14, 2002**

Dear Administrator Horinko:

The Hydroquinone Precursors and Derivatives Panel (HQPD) Diisopropylbenzene (DIPB) Task Force of the American Chemistry Council is pleased to submit the attached response to EPA's comments of April 8, 2003 on our initial test plan submission of November 14, 2002 for a category covering three chemicals (CAS Nos. 99-62-7, 100-18-5, and 25321-09-9). The attached response is provided on behalf of the following companies who are members of the DIPB Task Force: Eastman Chemical Company, Georgia Gulf Corporation, Goodyear Rubber and Tire Company, and Koch Specialty Chemical Company.

This submission includes the following documents:

- Item by Item Response to EPA's Comments of April 8, 2003 on ACC Panel's Original Submission of November 14, 2002;
- Revised Test Plan and Robust Summaries

This submission is also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
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Marian L. Horinko
HQPD DIPB HPV Chemical Challenge Program
September 26, 2003
Page 2 of 2

If you require additional information, please contact F. J. "Sonny" Maher, HQPD Panel Manager
at (703) 741-5605 or sonny_maher@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: DIPB Task Force

AMERICAN CHEMISTRY COUNCIL
Hydroquinone Precursors and Derivatives Panel
Diisopropylbenzene Task Force
Consortium Number
September 26, 2003

Item by Item Response to EPA's Comments of April 8, 2003 on ACC Panel's Original Submission
of November 14, 2002

SUMMARY OF EPA COMMENTS

The sponsor, the Hydroquinone Precursors and Derivatives Panel DIPB Task Force of the American Chemistry Council, submitted a test plan and robust summaries to EPA for diisopropylbenzenes dated November 14, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 4, 2002. The category consists of *m*-diisopropylbenzene (CAS No. 99-62-7), *p*-diisopropylbenzene (CAS No. 100-18-5), and mixed diisopropylbenzene isomers (CAS No. 25321-09-9).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals in this category is adequate.
2. Substance Definition. The submitter indicates that diisopropylbenzene (CAS No 25321-09-9) consists of a variable composition of ortho, meta, and para isomers. The submitter needs to provide ranges of typical percentage of each isomer in the mixture.
3. Physicochemical Properties. The data provided by the submitter for boiling point and vapor pressure are adequate for the purposes of the HPV Challenge Program. The submitter needs to correct some inconsistencies in the test plan, robust summaries, and references.
4. Environmental Fate. The data provided for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. The data for stability in water on the analog 1,4-diethylbenzene are adequate for the purposes of the HPV Challenge Program, but the submitter needs to augment the robust summary. The submitter needs to provide a robust summary with biodegradation data for *m*-diisopropylbenzene or for its analogue, and a technical discussion on the relative importance of *o*-diisopropylbenzene in the isomer mixture and its biodegradation potential.
5. Health Effects. EPA agrees with the submitter's Test Plan for meeting the health effects endpoints with the exception of chromosomal aberrations, reproductive, and developmental toxicity endpoints. EPA reserves judgment on the chromosomal aberrations endpoint pending receipt of additional information on cytotoxicity. EPA, however, tentatively accepts that no additional test data are needed for reproductive and developmental endpoints pending receipt of adequate robust summaries.
6. Ecological Effects. EPA considers the submitted acute data for fish and aquatic invertebrates inadequate for the purposes of the HPV Challenge Program. For algae, EPA reserves judgement on data adequacy pending submission of analog and SAR data in robust summary format.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE DIISOPROPYLBENZENE CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category to cover three substances consisting of *m*-diisopropylbenzene, *p*-diisopropylbenzene, and mixed diisopropylbenzene isomers. The first two members of the category contain >95% and >99% of their respective isomers, with other diisopropylbenzene isomers also present as minor components. The mixed diisopropylbenzenes contain variable proportions of the ortho, meta, and para diisopropylbenzene isomers. The submitter needs to provide typical ranges of isomeric composition, to the extent possible.

DIPB Task Force Response: Typical ranges of isomeric composition for diisopropylbenzene is included in the section “Summary of Test Plan and Data.”

Category Justification

The submitter adequately supports grouping the chemicals in the diisopropylbenzene category on the basis of their structural, physicochemical, environmental fate, and toxicological property similarities. Measured and estimated properties for the individual and mixed isomers support this grouping for the majority of the SIDS-level endpoints. The use of alkylbenzenes (cumene, ethylbenzene, diethylbenzene) as analogs for some SIDS-level endpoints is also supported adequately by the data and other evidence describing the physicochemical and/or metabolic similarities between these representative chemicals and the diisopropylbenzenes.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitter needs to specify the exact source for each value reported in table 1 (page 8) and indicate whether the value is measured or estimated.

DIPB Task Force Response: The table has been modified to reflect the fact that all values for the surrogate chemicals were obtained from the Hazardous Substances Database (HSDB). Information on the DIPB compounds is referenced in the robust summaries.

The data provided by the submitter for boiling point and vapor pressure are adequate for the purposes of the HPV Challenge Program.

Melting point. The data provided by the submitter for *m*-diisopropylbenzene, and *p*-diisopropylbenzene are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide the melting point data for the mixed isomer (CAS No. 25321-09-9) that were indicated as available on page 9 of the test plan in robust summary format.

DIPB Task Force Response: A robust summary for the value noted in Table 1 and noted in the test plan matrix as being available has been added.

Vapor pressure. The submitter needs to check its vapor pressure reference for the isomeric mixture (CAS No. 25321-09-9).

DIPB Task Force Response: The original reference noted in the robust summary was incorrect. The robust summary has been changed with the correct reference that had been identified in the HSDB.

Partition coefficient. In table 1 (page 8), the submitter reports log K_{ow} values of 4.9, 5.4, and 5.71 for diisopropylbenzene, *m*-diisopropylbenzene, and *p*-diisopropylbenzene, respectively (obtained from HSDB, estimation models and MSDS sheets), whereas on pages 20-21, it reports log K_{ow} values of 4.9, 4.9, and 3.45, respectively (estimated using KOWIN). The submitter needs to address this inconsistency.

DIPB Task Force Response: The data values in Table 1 are now consistent with those in the robust summaries. Furthermore, these values were updated with a newer version of EPIWIN.

Water solubility. In table 1 (page 8), the submitter reports a water solubility value of 1 ppm for the mixed isomers (CAS No. 25321-09-9), whereas on page 22, it reports a value of 4.325 (obtained from EPIWIN). The submitter needs to address this inconsistency.

DIPB Task Force Response: The data values in Table 1 are now consistent with those in the robust summaries. Furthermore, they were updated with a newer version of EPIWIN.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter needs to add to the robust summary the information that diisopropylbenzene category members do not have functional groups that are susceptible to hydrolysis.

DIPB Task Force Response: A statement has been added to the robust summary that diisopropylbenzene category members do not have functional groups that are susceptible to hydrolysis.

Biodegradation. On page 9 of the test plan, the submitter indicates that for *m*-diisopropylbenzene the endpoint is satisfied by using data from a structurally similar chemical. However, the submitter did not provide a robust summary with this information. The submitter needs to provide a robust summary with biodegradation data for *m*-diisopropylbenzene or its analogue. The submitter also needs to provide a technical discussion on the relative importance of *o*-diisopropylbenzene in the isomer mixture and its biodegradation potential.

DIPB Task Force Response: A brief robust summary has been prepared for meta-DIPB that indicates that data from para-DIPB and the mixed isomers of DIPB are being used as structural surrogates. The relative importance of *o*-DIPB in the mixture is unknown. However, since one of the biodegradation studies was conducted on the mixed isomers and the results indicated that essentially no degradation occurred, it is believed there was also little degradation of the ortho isomer.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data were submitted for the acute toxicity, repeated-dose toxicity, and gene mutation endpoints for purposes of the HPV Challenge Program. EPA also tentatively accepts that no additional test data are needed for reproductive and developmental endpoints, pending receipt of adequate robust summaries. However, the robust summary for the chromosomal aberrations endpoint for diisopropylbenzene lacked sufficient detail to fully evaluate the study.

Genetic Toxicity (chromosomal endpoint). EPA considers studies conducted using a mixture having a minor proportion of diisopropylbenzene (historically 25-40%) inadequate because the exact composition of the tested material is unknown and most of the mixture is undefined. For the *in vitro* chromosomal aberrations test, EPA reserves judgment on its adequacy pending submission of information on the cytotoxic concentration and/or the reason for selecting the dose levels used in the study.

DIPB Task Force Response: The genotoxicity studies conducted using “DIPB Feedstock / Cumene Tower Bottoms” were noted to contain from 25-40% DIPB isomers. These were well-conducted and documented studies and are thus important to include as supporting data. These endpoints were also filled using data from studies conducted with material containing the mixed isomers in a “pure” form.

The requested cytotoxicity data were not noted in the original reference utilized to create our robust summary and accordingly, were not reported in the robust summary. A note has been added to the robust summary indicating the absence of cytotoxicity data. However, the Panel believes that because the study was noted as having followed OECD guidelines, and OECD guidelines indicate the need for cytotoxicity testing and use of duplicate cultures, it should be assumed that cytotoxicity assessments were completed and the studies should still be deemed as reliable with restrictions. A copy of the information used to derive the summary has been attached.

Reproductive Toxicity. The submitter needs to provide robust summaries for studies on analogs that are described in Appendix 1 and the two studies by Elisuisakaya (1970a,b). EPA was able to retrieve an abstract on one of these studies (TOXLINE, Secondary SourceID:HEEP/72/02289). Although it may not contain core data that would be requested by OECD Guidelines, the rat study provides important evidence of the potential reproductive toxicity of diisopropylbenzene. Effects reported in the abstract include disturbed estrus cycles, decreased capacity for conception, decreased number of offspring, and decreased offspring weight (Elisuisakaya, 1970a). The analog data discussed in the literature review report did not show the reproductive effects, whereas the sponsored chemical did.

DIPB Task Force Response: Mr. Schardein had reviewed the data described within the Elisuisakaya (1970a,b) reports prior to the conduct of his review on the surrogate data used to support the category. His conclusions are noted on page five within the Appendix, and the panel relies on those conclusions to characterize this endpoint. Because the Elisuisakaya studies were deemed to be of low validity, they were not included in his overall developmental reproductive toxicity assessment for the category.

Developmental Toxicity. The submitter needs to provide robust summaries for studies on analogs that are described in Appendix 1.

DIPB Task Force Response: Narrative summaries of the several studies used to satisfy this endpoint can be found in Appendix I, entitled “The Use of Various Mono- and Di-Alkylbenzene Surrogates for the HPV Candidate Diisopropylbenzene Chemicals in SIDS Reproductive/Developmental Toxicity Testing” by Mr. James Schardein. In addition, summaries will be, or are currently, available in various other public documents. These include the OECD SIDS dossiers for Cumene (isopropylbenzene), ethylbenzene, and 1,4-diethylbenzene, as well as the summaries being prepared for the mixed isomers of diethylbenzene (CAS# 25340-17-4) sponsored in the ICCA HPV program.

Ecological Effects (fish, invertebrates, and algae).

The submitted acute toxicity data for fish and invertebrates are inadequate. For fish and invertebrates, each test was conducted at one test concentration only and either below the water solubility limit of the test substance using the measured concentrations or at the water solubility limit of the test substance using the nominal concentrations. Therefore, the results were insufficient to determine the toxicity of the test substances. For algae, the submitter did not provide the analog data in robust summary format or the input values for the SAR data submitted. EPA reserves judgement on the adequacy of the algal data pending submission of analog and SAR data in robust summary format.

DIPB Task Force Response: In regard to the acute fish and invertebrate toxicity tests for m-DIPB and p- DIPB, both were conducted using a flow-through, recirculating elutriation system designed to expose the organisms to an exposure concentration at or near the solubility of the test substance. Results of an unpublished 96-hour volatility study on m-DIPB indicated that the substance is extremely volatile in water with 100% of the material lost over 96-hours from a 1.9 mg/L solution. Therefore, the measured concentration of m-DIPB (0.93 mg/L) was the result of the low solubility and high volatility of the test substance, but reflected the most effective experimental flow-through design to maximize the exposure concentration. The toxicity test on p-DIPB was conducted in a similar manner. Therefore, these tests were conducted using the most effective experimental designs available for the physical/chemical characteristics of the test substances and do not warrant repeating. More methodology detail has been added to their robust summaries to better describe test conditions.

The Panel also believes that if chronic toxicity data are required, such data already available on some of the surrogate chemicals could be used in lieu of further animal studies on DIPB moieties.

In regard to the algal toxicity endpoint, summary information on the analog data (cumene and 1,4-diethylbenzene) are already available to the EPA and public from the OECD SIDS process (both chemicals) and within the IUCLID database (cumene). Robust summaries for the EPIWIN modeling data on the DIPB category members for algal toxicity have been prepared and updated using EPIWIN v3.10.

EPA suggests that the submitter conduct a chronic daphnia test instead of acute tests because the log Kow values for these chemicals are greater than 4.2.

DIPB Task Force Response: The Panel believes that if chronic data are required in the future, information already available on cumene and 1,4-diethylbenzene (analog chemicals utilized as surrogates for the mammalian toxicity endpoints) provide useful alternatives to support this endpoint.

Specific Comments on the Robust Summaries

Generic comments

The following comments apply to all of the robust summaries provided by the submitter. The submitter needs to confirm that internet hyperlinks are correct.

DIPB Task Force Response: The internet links have been changed since the data have been submitted, and some of the sites are being re-constructed. Accordingly, the links have been removed. Attached are the original reports downloaded from the sites.

Each summary should clearly identify the component percentages in test mixtures for each chemical or class. Studies that tested mixtures that were undefined or contained only a minor fraction of diisopropylbenzene are not acceptable for the purposes of the HPV Challenge Program.

DIPB Task Force Response: The genotoxicity data on “DIPB Feedstock / Cumene Tower Bottoms” is only included as supporting data as these endpoints are also filled with data from other studies.

Physicochemical Properties

Vapor pressure. The submitter’s 0.25-0.39 mm Hg value for the isomeric mixture could not be found in the Lide reference quoted on page 19 of the robust summaries. The submitter needs to check this reference.

DIPB Task Force Response: The data reported in the robust summary was obtained from HSDB and the reference for this data was incorrectly reported in our original robust summary, it has been corrected in the new summary.

Health Effects

A robust summary for a chromosomal aberration assay in cultured Chinese hamster lung cells omitted the number of replicates and information on cytotoxic doses.

DIPB Task Force Response: The requested cytotoxicity and replicate number data were not noted in the data summary used to write our robust summary and therefore, was not reported. However, because the study was noted to have followed OECD guidelines, and because OECD guidelines indicate the need for cytotoxicity testing and use of duplicate cultures, the studies should still be deemed as reliable with restrictions. A copy of the information used to derive the summary has been attached.

Ecological Effects

Algae. The submitter needs to provide the analog data in robust summary format and input values for SAR data.

DIPB Task Force Response: The estimates derived from this model were based on default physical chemical value inputs. The summaries have been changed to reflect this. Robust summaries for the structural surrogates are available in the documents referenced in the robust summaries.